REPORT OF THE BLUE RIBBON PANEL

ブルーリボン委員会報告

REVIEW OF THE RADIATION EFFECTS RESEARCH FOUNDATION

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In April 1995 the Science Council of the Radiation Effects Research Foundation (RERF) issued a statement, considering it "appropriate and desirable that the scientific activities of RERF be assessed carefully and in depth by an outside expert group that has not been previously involved in RERF activities". The Council recommended that "a high-level international Committee of distinguished scientists be appointed to carry out an assessment of RERF's current and future scientific activities". The United States Department of Energy (DOE) and the Ministry of Health and Welfare of Japan (MHW) agreed to accept the recommendation to establish an international Blue Ribbon Panel and on 11 October 1995 they jointly appointed Professor Roger H. Clarke, Director of the United Kingdom National Radiological Protection Board, as its Chairman.

The Panel was composed of scientists representing diverse disciplines related to radiation research and public health. Individuals with experience in medicine, epidemiology, radiation biology, immunology, health physics, biostatistics, genetics and public health were nominated.

The Ministry of Health and Welfare and the Department of Energy nominated four members each; MHW nominated two Japanese and two third-country nationals while DOE nominated two US and two third-country nationals. The final composition of the Panel, shown at Annex I, was of a Chairman, two Japanese nationals, two US nationals, and four third-country nationals.

The Panel was charged with conducting a thorough review of RERF activities for the purpose of making recommendations regarding future research. Specifically the Panel was asked to focus on the following:

the content and quality of the current research programme,
what future research should be conducted,
an evaluation of the importance and merit of research conducted at RERF,
areas of research that could be conducted together with other institutions both in Japan and worldwide, and
an assessment of the scientific peer review process.

In addition, guidance was given to the Panel that it should:

identify areas to which RERF can contribute by providing other organisations in the world with its information and expertise or *vice versa*,
identify how the RERF data can be used to advance world-wide radiation research while protecting the privacy of the survivors and other people cooperating in the research studies,
consider how the health studies of aging survivors, second generation survivors, and survivors exposed to low-level radiation should proceed, and
provide any additional suggestions and assessments, as needed.

The original time schedule set for the panel by MHW and DOE was that it be appointed in October 1995, and would meet in March/April 1996 at Hiroshima and Nagasaki. Preliminary results would be presented to the Board of Directors meeting in May/June 1996 and the final report would be delivered to MHW, DOE and the Board of Directors by the end of July 1996.

In the event the Panel held its first meeting at RERF in Hiroshima from 4-7 February and in Nagasaki 7-8 February 1996. On the first day the Panel heard of the early history of the Atomic Bomb Casualty Commission (ABCC), the precursor to RERF, and visited the Hiroshima Peace Museum, after which a commemorative wreath was laid at the Cenotaph.

The Panel was welcomed to its formal session by the Chairman of RERF, Dr. Shigematsu. During the following days, presentations were made by the six Department Chiefs on their programmes in: Epidemiology, Statistics, Information Technology, Clinical Studies, Genetics and Radiobiology. Each presentation was followed by an informal session during which detailed discussions were held with a wide range of

Departmental staff so that the Panel could probe the depth of scientific and medical knowledge.

The Panel also received a presentation from a representative of the US National Academy of Sciences on the management of its review and oversight programme at RERF.

The Panel had the honour to meet Governor Fujita of Hiroshima Prefecture and heard of his tentative plans for the establishment of a Cancer Centre in Hiroshima which would have international links.

At Nagasaki the presentations and discussions centred on the two Departments of Epidemiology and Clinical Studies, after which one of the co-chairmen of the Science Council presented a summary of the Council's views.

The Panel held its second meeting at the Headquarters of the NRPB in the UK from 19-21 May 1996, during which time the content of the report was agreed upon. The report was finalised at the beginning of June 1996.

The RERF research programme forms the most comprehensive study of a large, well-defined population that includes all ages and both sexes subjected to an instantaneous and wide range of radiation exposures. Several major research foci have evolved over time. These currently include epidemiological studies of cancer mortality and incidence and non-cancer mortality among the atomic-bomb survivors; ongoing clinical follow-up with the collection of biological specimens and longitudinal clinical measurements and data on morbidity in a fixed subset of the survivor population; genetic and epidemiological studies of the children of the survivors; and application of modern molecular, cytological, physiological and other technologies to the unique biological samples provided by the survivors in order to identify radiation-induced changes and to investigate the underlying biological mechanisms of these changes.

Data on cancer mortality derived from the atomic-bomb survivors have become the primary source of cancer risk estimates. Other sources now largely provide substantiation of, rather than alternatives to, the atomic-bomb survivor-based assumptions. Worldwide, radiation protection standards for workers and the public are based on the survivor risk estimates, as promulgated in the 1990 recommendations of the International Commission on Radiological Protection. Risks associated with population exposures due to accidental radiation releases and individual exposures (for example, in probability of causation lawsuits) also are estimated based on atomic-bomb survivor data. RERF studies have shown that fetal radiation exposures affect physical and mental development and, as the *in utero* cohort ages, the nature of the excess

cancer risks in this group is being clarified. RERF is also the primary source of information on the occurrence and nature of genetic effects in humans following radiation exposure.

Basic biological research at RERF already has clarified issues previously which cannot be resolved by physical dosimetric and epidemiological approaches. With recent and continuing worldwide advances in molecular genetics, RERF should be able to play a unique and central role in determining radiation's effects at the gene locus level.

RERF is a unique research enterprise, studying an unparalleled population unlikely to exist again. At this juncture, there is an incomplete understanding of the late effects of radiation exposure during childhood and early adulthood while studies are just reaching a point at which important insights into the existence and nature of genetic effects can be gained. The follow-up of the Life Span Study (LSS) cohort of atomic-bomb survivors is the centre of the RERF epidemiology programme. The follow-up is based on the family registries which assure virtually complete ascertainment of death. *LSS Report 12* on cancer mortality among the LSS cohort from 1950 through 1990 emphasises how the excess cancer risks associated with radiation exposure depend on modifying factors such as sex, age-at-exposure, and attained age.

The genetics programme at RERF is the singular study worldwide on the genetic effects of irradiation in humans. An important part of the genetic studies is the ongoing epidemiological follow-up of mortality and cancer incidence on over 80,000 first generation (F_1) offspring , about 43% being born to exposed parents and the rest to non-exposed parents. The follow-up has been based on both death certificate-based mortality and tumour registry-based cancer incidence. Epidemiology as well as studies on congenital defects, stillbirths, sex chromosome abnormalities and reciprocal translocations have not demonstrated a significant radiation-related increase in any endpoint.

The Adult Health Study (AHS) operated by RERF and its predecessor, the Atomic Bomb Casualty Commission (ABCC), continues to be one of the largest and longest running clinical cohort studies in the world. During the 40 years of its existence, the AHS clinical programme has played a key role in obtaining and sustaining support for ABCC-RERF from the survivors and the local communities. The biennial AHS medical examination is the only part of the RERF programme that involves direct contact with survivors and thus serves as the main direct benefit that

RERF provides to the survivors. It is RERF's primary source of information for understanding non-cancer effects of radiation, although information is also available from the mortality follow-up of the LSS. Through the AHS, biological materials are collected which will become increasingly useful for molecular and other bio-marker studies of cancer and non-cancer diseases. Again, it is stressed here that the effects of radiation exposure on diseases other than cancer remain largely unknown. The RERF clinical programme is an irreplaceable source of biochemical and physiological measurements that underpins all of RERF's epidemiological analyses, including those of non-cancer disease incidence.

The health of over 200,000 people from Hiroshima and Nagasaki, covering both exposed and unexposed persons together with their offspring, has been under surveillance by RERF since the 1950s. Table 3.1 summarises the cohorts being followed and gives brief details about the way in which the subjects are being followed.

NAME OF COHORT	NUMBER OF SUBJECTS
Life span study (LSS) *	120,300
Adult Health Study subset †	22,400
In utero exposure *	3,300
Adult Health Study subset †	1,100
Offspring of the survivors (F_1 generation)	88,500
TOTAL	212,100

* All subjects are followed routinely for death and, within Hiroshima and Nagasaki Prefectures, for cancer incidence. In addition, information on lifestyle factors such as smoking, alcohol consumption, diet and reproductive factors has been collected on the LSS cohort in four postal surveys conducted in, or around, 1960, 1970, 1980 and 1990.

† Subjects in the Adult Health Study subset are routinely examined every two years and a vast amount of clinical data and biological specimens has been collected from these subjects.

The Life Span Study population followed at RERF is unique for many reasons. Firstly, it includes large numbers of subjects with well-documented information about their exposure to ionising radiation. Secondly, for most subjects there is detailed information of high quality

about personal characteristics (e.g. height and weight), and about habits (e.g. smoking, alcohol consumption and diet). For about 10% of the total population (i.e. the 22,000 people included in the Adult Health Study; see Table 3.1), clinical and biological characteristics are available. Thirdly, follow-up for cancer incidence and death has been continuing since the 1950s and very few subjects have been lost to follow-up. Finally, substantial numbers were exposed at young ages and, even though 50 years have elapsed since their exposure to radiation, the majority of these persons are still alive (see Table 3.2: among the approximately 86,000 persons with doses estimated under the DS86 Dosimetry System, about 31,000 of the 35,000 aged under 20 at the time of bombing were still alive in 1994).

AGE AT THE TIME OF BOMBING	NUMBERS IN 1950	APPROXIMATE NUMBERS ALIVE IN 1994
0-9	17,824	16,500 (93%)
10-19	17,557	14,700 (84%)
20-29	10,882	7,700 (71%)
30-39	12,270	5,000 (41%)
40-49	13,489	1,000 (8%)
50 +	14,550	<100 (<1%)

*Restricted to persons with estimated DS86 dose.

Although other populations have been exposed to ionising radiation since the bombing of Hiroshima and Nagasaki, in no other situation has it been possible to set up detailed studies of large numbers of subjects of all ages and both sexes, who have substantial exposures to radiation with such reliable information both on radiation exposure and on subsequent health. Furthermore, this is one of the very few populations in which it is possible to study the effects of known exposures at early ages when more than 50 years have elapsed since the exposure.

The population studies at RERF are unique not only because of the type of exposure received by such large numbers of subjects, but also because the quality of the information recorded about each individual is extremely high. It seems unlikely that a comparable opportunity to study the effects of ionising radiation on health in such a detailed way will present itself in the future: and even if it does, it will take 50 years to accrue as much information as now exists at RERF.

4. REVIEW OF THE SCIENTIFIC PROGRAMME

General comments

In reviewing "the content and quality" of the Radiation Effects Research Foundation's scientific studies, the importance of this large group of research projects cannot be overestimated. Its importance lies in the uniqueness of the survivor cohort under study and in its central role in assessing radiation carcinogenesis and providing the basis for radiation protection standards throughout the world. It furnishes an as yet unfinished landmark study of radiation effects in humans that, it is hoped, will never be feasible again. The very nature of a large amount of the research done at RERF in epidemiology, in genetics, and in the Clinical Studies Programme requires that it is necessarily systematic and unchanging in character.

The lifetime attributable cancer risk for radiation exposures in childhood is one of the most important unresolved problems of radiation protection of the population, and at present it is based on uncertain assumptions. Future observations at RERF are necessary to resolve this question. These observations will have to continue for several decades, when those who were exposed as infants will have reached the age of highest cancer rates.

Risk estimates for radiation-induced cancer have in the past been based predominantly on the cancer *mortality* data and their analysis at RERF. The recent extensive work on cancer *incidence* has added a second and

equally important base for risk modelling and thus for the derivation of nominal risk factors.

The scientific programme is reviewed in six topic areas, Epidemiology, Statistics, Information Technology, Clinical Studies, Genetics, and Radiobiology, in each of which work is undertaken at Hiroshima. The programmes at Nagasaki are in Epidemiology and Clinical Studies and are reviewed together with the work in those areas at Hiroshima.

Epidemiology

The main responsibilities of the two Departments of Epidemiology are:

- the follow-up of the Life-Span Study (LSS), persons exposed *in utero* and F_1 (i.e. children of exposed subjects) cohorts for deaths and cancer registrations ;
- the maintenance of tumour and tissue registries in Hiroshima and Nagasaki;
- in-depth studies of the relation between radiation exposure and other lifestyle factors in the aetiology of disease.

Overall the Departments of Epidemiology are responsible for the follow-up of about 200,000 people. The largest group being followed are members of the Life-Span Study (LSS). So far about 8,000 cancers have occurred among the members of that population with DS86 doses; and about 20,000 tissue specimens are held from surgery and autopsies. Lifestyle information for most of the LSS population has been collected from four postal surveys carried out at about 10 yearly intervals, in approximately 1960, 1970, 1980 and 1990.

Staff in the Departments of Epidemiology, working closely with staff in the Department of Statistics, have contributed to regular reports on deaths in the LSS population in relation to radiation exposure. As the mortality data have accumulated, these reports have evolved from a relatively straightforward presentation of tests for radiation effects to detailed analyses and characterisation of factors that affect the risk of death from cancer or other causes. The most recent report (*LSS Report 12*) addresses cancer mortality between 1950 and 1990. The excess

relative risk per unit dose has been estimated for 12 solid cancer sites for which there were at least 100 deaths. For most of these cancer sites there has been a statistically significant increase in risk associated with radiation exposure. Furthermore, the data for many of the solid cancer sites are consistent with a common value for the excess relative risk.

The mortality data for all solid cancers combined show a remarkably linear dose-response over the range 0-3 Sv, whereas for leukaemia the trend in risk with dose is non-linear with an upward curvature. While most of the excess leukaemia risk occurred in the first 15 years following exposure, the absolute excess rate for solid cancers increased during the follow-up in a manner that is roughly proportional to the increase in background rates with increasing age. The excess relative risk tends to be higher for exposure in childhood than in adulthood, and is higher for females than for males for most non-sex-specific cancer types. However, the age-specific excess absolute risks generally depend little on sex or age at exposure.

The earliest programme for monitoring cancer incidence in the atomic bomb survivors grew out of efforts initiated in the late 1940s to register leukaemia and other haematological disorders. With the cooperation of medical associations in the locality, population-based tumour registries were established in 1957 in Hiroshima and 1958 in Nagasaki. These registries have been operated by staff at ABCC-RERF since their inception and are generally regarded as the best tumour registries in Japan. Data on cancer incidence in the LSS up to 1987 formed the basis of comprehensive reports published in 1994. These data represent an important complement to the cancer mortality data; despite the shorter follow-up period for solid cancer incidence, the number of cancer cases is greater than the number of deaths. Furthermore, the incidence data provide risk estimates for cancers with relatively low fatality, such as those of the breast, thyroid and skin, and clarify the examination of cancers for which death certificate information is often incomplete or inaccurate (eg. liver cancer). Work on cancer incidence in the LSS is continuing with a series of detailed site-specific studies.

The previous LSS follow-up indicated some association between non-cancer mortality and radiation dose. This topic has been studied as part of the Adult Health Study (see section 4(iv)). In addition, a report based on the extended mortality follow-up is being prepared. Follow-up of those exposed *in utero* has indicated a possible increase related to radiation, although based on a small total number of cases. In contrast, no

statistically significant trends with dose in mortality or cancer incidence have been observed in the F_1 cohort. As well as the continuation of these investigations, studies of familial aggregation of cancer in members of the LSS cohort are being planned.

The cohorts being followed by the Departments of Epidemiology are among the largest and best documented in the world. Even if it were not for the unique exposure to ionising radiation of the population, the value of the information collected about lifestyle and health over such a long period of time is virtually unrivalled elsewhere. The epidemiology programme is central to the work of RERF. There is a great deal of interest in the effects of various aspects of Japanese lifestyle on health (especially dietary factors) and on the effects of the changes in lifestyle over the last 50 years. To make full use of the scientific data already held within RERF, a substantial additional epidemiological effort would be required. Collaboration with epidemiologists from within Japan and abroad, especially on exploring some of the aspects of the data that do not relate directly to radiation exposure, should be of great benefit to all concerned.

The data held by the Departments of Epidemiology are of enormous importance, not only for assessing the effects of radiation on health, but also for determining the influence of various lifestyle factors on health and their interactions with radiation exposure. There is currently insufficient effort available to analyse the data and present reports, and much of the potentially valuable information collected has so far not been fully utilised.

We recommend that the Departments of Epidemiology should continue to collect data on mortality and cancer incidence, and that they be strengthened. The management of RERF should give these studies the highest priority in view of the size and scope of the data. In addition, research should be carried out by collaborating with epidemiologists from other institutions both in Japan and elsewhere, so that the full range of potentially valuable information already collected can be analysed.

(ii) STATISTICS

The Departments of Epidemiology and the Department of Statistics are closely interlinked and jointly form the *central core* of RERF. Their tasks are specific and indispensable to the continuing follow-up of the A-bomb survivors and other aspects of the research programme.

The most recent studies of cancer amongst the survivors have provided information that supports modified risk models, intermediate between the so-called absolute risk models and the relative risk models. The continuation of this work and the growing need to interlink analyses from the mortality and the incidence data will - beyond the obvious extension of the epidemiological efforts - require a broadened and stabilized team of scientists in the Department of Statistics.

Through its extensive body of work on the A-bomb survivors the Statistics Department at RERF has had great influence on other radiation studies worldwide. Recently the Department began a very active cooperation with the radioepidemiological investigations on the highly exposed nuclear workers of Mayak in the Southern Urals and on the population of the villages on the contaminated Techa river in the former Soviet Union. These two studies deal with the health effects resulting from *continued exposures* and will, thus, be an essential complement of the studies on the atomic-bomb survivors who were subject to *exposure over a short time*. The new studies can largely be patterned on the work done on the A-bomb survivors, and this will give important feedback and added importance - but also added responsibilities - to the programme of RERF.

The Departmental staff in conjunction with collaborators have developed the software package EPICURE which is currently used worldwide for the analysis of epidemiological data. It is important that the development of this software be continued because it facilitates comparability between different studies.

The work on cancer mortality and incidence has been the subject of extensive publications, and for a number of years now - in a significant departure from earlier policies - well-documented basic data sets have been made available for analysis by other groups. For work on malformations due to prenatal exposure - and specifically the important observations on mental retardation and the reduction of IQ - similar progress has not yet been achieved. Important analyses have been performed, but the statistical treatment has been less systematic, and

publications are less complete. The basic data sets - for example on the results of intelligence tests and other studies on the prenatally exposed - have not yet been made available outside RERF.

CONCLUSIONS

Highly successful work has been performed in the Department of Statistics, which is a source of great strength for the entire organisation. Its input has been essential in making the accumulated data sets the worldwide basis for the estimation of human radiation risks.

RECOMMENDATION 2

We recommend that the Department of Statistics should continue to produce analyses of the risks of radiation exposure in collaboration with the Epidemiology Departments and that the high quality of the research in the Statistics Department be maintained.

RECOMMENDATION 3

We recommend that the Department of Statistics should continue to make available basic data sets on mortality and cancer incidence for analysis by other groups. This should now be extended to making available those data sets relating to mental retardation, IQ, and related outcomes of exposure *in utero*.

(iii) INFORMATION TECHNOLOGY

The Panel received an informative presentation from the Information Technology Department, in which it learned that for most of RERF's lifetime, data associated with the separate research programmes have been maintained on a series of mainframes and often analysed using specialised software, which has had to be developed within the organisation.

It was recognised by the late 1980s that the increasing power and decreasing costs of PCs and RISC based workstations, together with the availability of much general software for inter-computer communications, database management, data analysis and graphics pointed to a move from mainframe computing to a distributed network. A major programme was therefore begun in 1991 to install an integrated system of networked IBM-compatible PCs and Unix workstations, and at the end of 1994 the previous mainframe was removed.

This change in direction has brought many advantages to RERF. Internal communications within RERF - including communications between Nagasaki and Hiroshima - are much improved, access to Internet and its facilities are available and RERF can now use readily available commercial software packages for business management. In addition, the individual PCs can readily manage much of the statistical analysis, data handling and graphics associated with particular projects on a stand-alone basis.

In practice, it has turned out that the move to a distributed network has led to significant economies and the present system, which is overall more powerful than its predecessor, has been less expensive, both to install and to maintain.

Perhaps the most important innovation has been the installation of a new relational database in the Unix environment, and the transfer to it of the major data files such as the Master File, the tumour registry, tissue registries, the LSS and the DS86 dosimetry. Apart from eliminating many redundancies, this amalgamation of data from overlapping research programmes greatly facilitates the capture into working files of all available information on cohort members for subsequent analysis and study.

There is still much to be done to include further data still held in independent files, so that all relevant data on individuals can be assembled efficiently, and we understand that further incorporations are

in train. At the same time, the discipline of operating within a single coherent database system is seen to be helpful in that it requires close and careful scrutiny of the various data sources in order that they may be included in a systematic way. At the end of the day, this coordination of all of RERF's major data holdings within the one system should lead to a richer and more robust body of data for the cohort studies in general.

From the perspective of research outcomes, the Panel believes that the changes to the computing environment will enhance the quality of the studies and open up ways in which any new directions may be followed in an efficient manner.

The Information Technology Department, in its presentation to the Panel, acknowledged that there are still many things to be completed in support of RERF's research and appears to have a clear sense of direction in its future planning. Its members also pointed out that the introduction of a new and unfamiliar system has required them to enhance their user support and to provide training and assistance when users encounter difficulties.

CONCLUSION

Efficient data management and computing are the backbones to the success of research at RERF. The Panel believes that RERF has taken the right strategic decisions with respect to computing infrastructure, and the Department has gone about implementing them with considerable skill and intelligence. Impressive progress has been made over the last few years in creating a central linked database.

RECOMMENDATION 4

We recommend that strong support continue to be given to the Department of Information Technology because it is essential that the large body of data collected over many decades is properly stored, documented and accessible to researchers at RERF.

(iv) CLINICAL STUDIES

The Clinical Studies Research Programme is based largely on the Adult Health Study (AHS), the cohort of about 20,000 out of the Life Span Study (LSS) of 120,000. Since 1978, about 2400 Life Span Study participants and 1000 *in utero* exposed persons have been added to this sample. Every other year, all participants are examined in detail, including history, physical examinations, ECG, chest x ray, ultrasonography, blood tests, etc. Other data, such as information on lifestyle and results of special tests including bone density and gynaecologic examinations, are also collected.

The necessarily repetitive nature of many of the research projects was apparent in the presentations to the Panel. Many of the current projects are very much like those of yesterday; some essentially provide further documentation of prior findings. Yet this kind of organised, iterative, systematic, and meticulous study and clinical follow up is essential to fulfil the goal of providing a precise database for determining cancer risk estimates and for exploring non-cancer diseases associated with radiation exposure. Like the Life Span Study, the Adult Health Study derives its importance from the unique value of the survivor cohort.

An important function of the Clinical Studies Programme is to bind the exposed populations in Hiroshima and Nagasaki to the Radiation Effects Research Foundation and its scientific programme. The AHS is literally the only systematic link of RERF with survivors; it provides them with a visible service, one which they obviously value, as indicated by the high level of voluntary participation. The biennial medical examinations of the AHS cohort also provide elements of medical social work - support, attention and respect - without which it seems doubtful that the full cooperation of the surviving populace of the two cities could be attained. The AHS should be considered as one of the important measures directly beneficial to the health of the survivors.

The contributions of the AHS may be described in three broad categories:

studies that augment, enrich or supplement the findings of the Life Span Study by supplying additional clinical and laboratory data on cancer and on potential contributing factors and/or confounders in the aetiology of disease;

studies that focus on issues other than the central focus of the Life Span Study: in particular, the detection and analysis of the effects

of radiation that cannot be studied through mortality or cancer incidence data; and

the provision of biological materials essential to other investigations at RERF.

A major function of the clinical programme is the early detection of carcinoma in the AHS. Furthermore, a unique contribution of the AHS lies in its exploration of the possible associations between radiation exposure and diseases other than cancer. The non-cancer AHS studies may be grouped into three categories: those in which significant radiation-related effects have been established; those in which suggestive (but not definitively established) radiation-related effects have been noted; and those in which no radiation-related effects have been found.

Significant radiation-related effects to those exposed *in utero* were manifest in small head size and mental deficiency. In addition, brain damage has been found in severely mentally retarded individuals examined later in life and exposed *in utero* between the eighth and fifteenth week of gestation. A significant and dose-related increase in the incidence of uterine myomas has been found among the survivors, as well as a significant and dose-related increase in the incidence of parathyroid adenomas. Lenticular opacities, which are well-known to be radiation-induced, were found in increased incidence in this population in studies conducted twenty years ago. An update is planned. It is desirable - and also urgent in the view of the aging of the survivor cohort - to conduct more sophisticated cataract studies.

Suggestive radiation-related increases in cardiovascular disease incidence, specifically the incidence of myocardial infarction, cerebral infarction, and the prevalence of aortic arch calcification and systolic hypertension require further studies to confirm a real association between radiation exposure and atherosclerosis. Similarly, suggestive increases in the incidence of thyroid adenomas and chronic liver disease in the exposed population have been noted in AHS studies, although the latter finding may reflect a high level of hepatitis virus infection. In another study, the onset of menopause has been found to occur earlier among the heavily exposed survivors than among the unexposed; analysis of serum FSH and oestrogen levels in the remaining premenopausal women is under way.

No increases have been found in mortality or incidence of congenital abnormalities in the F_1 progeny, although no systematic clinical examinations have occurred since the first year of life in this group. Both dominant disorders and multifactorial inherited diseases frequently are manifest after the first decade of life and, in the latter case, usually after adulthood. Further study of this cohort is essential; while under the Genetics Department, it would require the direct participation of the Clinical Studies Programme. Studies of thoracic vertebral fracture have shown no correlation with radiation exposure. Studies of senile dementia are under way, as is an evaluation of physiological measurements in more than 8,000 AHS participants as a predictor of mortality or morbidity associated with aging. Accelerated aging has not been demonstrated.

The Clinical Studies Programme maintains a collection of 110,000 frozen serum samples and 11,000 plasma samples spanning the last thirty years of the programme; in addition, there are 13,000 lymphocyte samples for the Department of Radiobiology, which maintains its collection in liquid nitrogen. These and other samples will make possible the retrospective determination of potential confounding factors and contribute to special studies of the immune system. Further, the Clinical Studies Programme has been involved in obtaining the cell lines from 800 families - 1600 parents and 1200 children - for a major project to screen DNA samples from parent-child trios. This is the largest fixed cohort population in the world for the detection of radiation effects on human germ line mutations. Finally, the Clinical Studies Programme is involved in providing the teeth essential for dosimetry studies based on electron-spin resonance of tooth enamel.

CONCLUSIONS

The importance and merit of the research lies largely in the size and quality of follow-up of the LSS and AHS populations, the quality of the epidemiology and statistics as they relate to the LSS and AHS groups, and the continuing assessment of *in utero* exposed survivors. The role of the Departments of Clinical Studies is central to attaining many of the goals of all divisions.

The content and quality of the research lies in the collaborative role that the Departments play with all other Departments:

by providing clinical data on fatal and non-fatal carcinomas and on non-cancer effects of radiation exposure;

by enabling in-depth investigations of associations to be observed in the LSS;

by furnishing a unique pool of serum, plasma and lymphocyte samples; and

by providing an essential "bridge" function to the survivors.

We recommend that while many of the Clinical Studies projects under way should be extended, the programme should be critically reviewed so that those which are not promising are discontinued. The continuing surveillance of the cohort who were children in 1945 and are now adults is likely to be revealing, since radiation sensitivity may be highest in the young.

We recognise that the AHS is vital to the wellbeing of the survivors and we recommend that this important service continue, since we believe it has led to their high level of cooperation with RERF. As the population ages and health problems become more complex, consideration needs to be given to ensuring that the voluntary participation remains high.

GENETICS

The Genetics Department aims its work at two major issues. The first and traditional task has been the assessment of hereditary damage in the offspring of the A-bomb survivors. A second task is the work in cytogenetics and more recently in other biological dosimetry, in order to reconstruct doses and/or to assess the validity of the DS86 dosimetry system.

[illegible]

Extensive studies of untoward pregnancy outcomes, mortality exclusive of cancer, malignant tumours in the first two decades of life, cytogenetics, and protein biochemical genetics in the children (F_1 generation) of the A-bomb survivors have shown no evidence of excess. This led to the initial conclusion that human sensitivity to these effects appears to be substantially less than those derived in early studies on mice. Recently the mouse data were critically reassessed, and it is now uncertain whether humans are, in fact, substantially less sensitive than the mouse to the mutagenic effects of ionising radiations.

As a consequence of unresolved judgements on the animal data, it is uncertain whether risk estimates for radiation-induced hereditary damage can be based on animal studies. For this and other reasons, full use must be made of the potential insights that can be obtained from the observations in families of A-bomb survivors. Recent work in the Genetics Department is focusing on studies in molecular biology that utilize immortalized B-lymphocyte cell lines, to discover differences in mutation rates between 500 families with exposed parent(s) and an equal number of control families without exposures. Innovative new techniques (e.g. the examination of mutations at mini-satellite loci) have been employed on a pilot basis in these studies but have not, up to now, demonstrated enhanced mutation rates in the exposed genomes. All of these studies are based on rapidly evolving techniques of molecular biology and thus must be considered as initial efforts. Future developments in molecular biology should permit far more complete analyses. They might ultimately allow the precise assessment to be made of molecular changes in the genome of family members.

The exposed population

Cytogenetic studies have long been an important part of the work of RERF and its predecessor organization. In earlier times, they were restricted to the determination of unsymmetric chromosome aberrations - such as dicentrics. As these aberrations are 'unstable', i.e. incompatible

with cell proliferation, they have only limited persistence of, typically, a few years. Although important questions were still unresolved - especially the apparently different dose dependencies in Hiroshima and in Nagasaki - it has become, therefore, less attractive in the recent past to invest work in these studies.

The advances of molecular biology have changed the situation and have given new momentum to the work in biological dosimetry with chromosomes through the technique of FISH (*f*luorescence *i*n situ *h*ybridization). This work has made it possible, by now, to determine symmetric, i.e. stable, chromosome aberrations, without excessive investment of manpower. This Department has taken effective leadership in the development and practical use of the FISH technique which allows retrospective biological dosimetry for exposures that occurred many years ago.

The Genetics Department has also taken the initiative to make the FISH technique available to Russian scientists working at Mayak and at the Techa river. Together with the involvement of European groups, this has led to an international network of cooperation for the intercomparison and improvement of cytogenetic methods. In view of various aspects of the FISH technique that are still unresolved, it is essential that the current intercomparisons and the joint application of the new methods to various exposed populations be continued and even extended. This relates to the A-bomb survivors, the nuclear workers at Mayak, the Techa river populations, the populations subjected to fallout from the Semipalatinsk nuclear tests, and certain groups that have been exposed after the Chernobyl accident.

This Department has put into practice improved techniques of ESR (electron spin resonance) dosimetry, specifically on teeth. This approach complements the cytogenetics results and it is, therefore, justified that the ESR dosimetry studies be given equal priority. While it is essential that the best techniques be used, there is no requirement for separate methodological work in the group; it is, therefore, appropriate that the Department has established external links to share new technical developments, especially the use of dentin in addition to the tooth enamel.

Parallel applications of the two techniques, FISH dosimetry and ESR dosimetry, to A-bomb survivors and other exposed groups have shown that the chromosome studies will gain greatly from the intercomparison of the results. The tooth dosimetry studies will be restricted to fewer

cases, but they appear to be applicable to lower doses and are subject to less variability; they can, therefore, serve as an added 'calibration' that sharpens the results of the chromosome studies.

CONCLUSIONS

While molecular biology investigations will enable the most detailed determinations to be undertaken and will thus be the focus of future work, there is nevertheless need to continue - and even to extend - the more conventional studies of the health of the offspring (F_1 generation). They will also have continued importance because it remains uncertain at what point molecular studies can come sufficiently close to the resolution of the problem of multifactorial hereditary damage produced by radiation.

It does now appear that there can be a more complete chain linking the evolving physics dosimetry and individual data on location at the time of the bombing to chromosome data, to tooth data, and data from solid state dosimetry on other objects, such as building materials, ceramics, or jewellery. While dosimetry has traditionally not been the task of RERF, these new interconnections will be very important for validating the DS86 dosimetry system.

RECOMMENDATION 7

We recommend that the studies on the health of the offspring (F_1 generation) of the survivors continue, since they may elucidate data on multifactorial disease while also providing direct benefit to the survivors and their offspring.

RECOMMENDATION 8

We recommend the preservation of biological samples for FISH analysis and for ESR, together with the documentation that will be needed to compare dose estimates based on biological samples with those from physics assessments.

RECOMMENDATION 9

We recommend the continuation of the storage of biological materials and associated documentation for future molecular genetic studies.

RECOMMENDATION 10

We recommend that the most advanced methods and expertise in cytogenetics continue to be available at RERF.

RADIOBIOLOGY

The Department of Radiobiology is a comparatively recent branch of RERF. It has been established to ensure that full use is made of the singular biological material available to RERF, especially the potential for performing molecular biology studies of familial relations in A-bomb survivors, their children and grandchildren. Work is being performed on molecular oncology, on immunology and on somatic mutations. The latter is to, some degree, interlinked with the efforts of the cytogenetics group on biological dosimetry. The studies on molecular oncology and immunology are closely related, because they are primarily directed towards the elucidation of the molecular and cellular steps in the process of carcinogenesis.

One of the most significant developments in radiobiology and generally in radiation research is the emergence of what may be called *molecular epidemiology*. It is still uncertain whether there are molecular markers, i.e. gene alterations, that are specific to - or that tend to be correlated with - certain causative factors, such as ionizing radiation. Molecular biology studies with this aim are now conducted in many laboratories worldwide. If specific markers can be found, radiation epidemiology will have an entirely new basis. Obviously this would be of central importance to the core programme of RERF. The archives of tumour and normal tissue material from A-bomb survivors are of greatest importance in view of these developments, and the extension and up-keep of the repositories is a central task for RERF. It is also essential that full expertise be available at RERF for adequate planning and for utilization of any methods that may become practicable. The radiobiology programme has met this challenge successfully. It is particularly important that it has been examining the methods to utilize archival material from autopsies more than 40 years old and that it has, in fact, demonstrated that gene amplification works as well with this material as with fresh probes. A variety of known oncogenes and tumour suppressor genes has been examined in current studies, which attests to the expertise of the research group.

Better insight into the function of the lymphocyte system will be a precondition for untangling the mechanisms of carcinogenesis. Important questions are still unsolved and it is therefore appropriate that RERF utilizes its specific wealth of information to contribute to the required investigations. The particular strengths of the studies at RERF are the

repeated observations in groups of A-bomb survivors that extend over sufficiently long periods to demonstrate the effects of aging, and the combined effect of aging and radiation exposure on the immune competence of T-cells. Very little is still known about the clonal expansions that originate from individual normal and stem cells. Recent studies at RERF on clonal expansion are, therefore, of special interest; these studies show that one and the same chromosomal aberration can appear in substantial fractions of T-cells, B-cells, erythroid progenitor cells and myeloid progenitors. Such studies may become the singular basis of much improved quantitative knowledge of the kinetics of the haematopoietic system. They can be the focus of important international cooperation using the observational material available only at RERF.

Somatic mutations at three different gene loci, HLA, TCR, and HPRT, are being studied as possible instruments of an alternative form of biological dosimetry. It appears that these systems are applicable when exposures are recent, while the mutations are not sufficiently persistent to provide reliable information on exposures that occurred a number of years ago or in the more distant past. There are indications in some of the studies on the A-bomb survivors that determination of the erythrocyte glycophorin A mutation (GPA) is more promising as a method to determine past exposures. But, as a whole, it would appear that FISH in lymphocytes and, in particular, ESR in teeth are superior approaches for biological dosimetry. The study of somatic mutations may still be justified in view of possible but still unknown future advances, but it does not appear to have special priority at this point.

The archives of tumour and normal tissue material for molecular and biological studies from A-bomb survivors are of great importance in view of developments in molecular biology, and the extension and upkeep of the repositories is a central task for RERF.

The particular strengths of the immunology studies at RERF are the repeated observations in groups of A-bomb survivors that extend over sufficiently long periods to demonstrate the effects of aging, and the combined effect of aging and radiation exposure on the immune competence of T-cells. Recent studies on clonal expansion are of special interest.

Somatic mutation systems are applicable for biological dosimetry when exposures are recent, but the mutations are not sufficiently persistent to provide reliable information on exposures that occurred in the distant past.

The establishment of causality in epidemiological studies requires several conditions in addition to a strong association. Among these conditions the postulation of a "plausible mechanism" is essential. This postulation, in the form of a mechanistic model, is also the basis for extrapolations beyond the observations, particularly at very low values of the cause.

It is clear, therefore, that RERF radiation risk studies will always be related, explicitly or implicitly, to mechanisms and models. The spectacular increase in the understanding of the cancer process on the basis of molecular genetics indicates that models will evolve in this direction. While it does not seem appropriate to specifically include modellers in the staff of RERF, it would be very important that the implications of data from experimental studies are kept under review as they may influence the research strategy of the Foundation.

We recommend that the Department of Radiobiology should focus on molecular epidemiology and immunology and that strong links should be forged between RERF and the relevant groups around the world involved in modelling the carcinogenic process.

LSS Report 12 highlights the uncertainties associated with the current internationally recommended estimates of radiation induced cancer risk, especially for those exposed as children. The evidence to date suggests that solid cancer excess risks are likely to persist and that excess rates will increase throughout life. Excess relative risks for solid cancers among those exposed as adults have remained fairly constant throughout their lifetimes. For people exposed in childhood, there is some evidence that relative risks have declined slightly; however, excess rates (ie absolute risks) for this group are increasing with age in a manner consistent with the increases seen for those exposed as adults. For those exposed as children, the total number of cancer deaths is currently small; however, this number is doubling every 5 years, and estimates of the number of excess cases are increasing at about the same rate.

Although lifetime follow-up is essentially complete for those exposed when older than age 50, more than half of the LSS cohort and over 90% of those exposed as children are alive now. Table 5.1 gives both the actual and projected numbers of persons in the cohort. By the year 2000, the number of cancer deaths among those exposed when younger than age 20 will be 3 to 4 times that seen up to 1990 and will continue to increase rapidly throughout the first 10 to 15 years of the next century. Therefore continued follow-up of those exposed as children or as young adults is essential to the understanding of radiation-induced cancer risks in this cohort.

TABLE 5.1 LSS COHORT* SIZE, 1950-2020

	YEAR							
	1950	1990	1995	2000	2005	2010	2015	2020
AGE AT EXPOSURE (y)								
0-9	17,824	16,768	16,450	15,990	15,290	14,280	12,710	10,390
10-19	17,557	15,163	14,500	13,540	12,040	9,800	6,780	3,620
≥ 20	51,191	16,971	12,800	8,910	5,430	2,710	970	100
Total	86,572	48,902	43,750	38,440	32,760	26,790	20,460	14,110
AVERAGE ATTAINED AGE								
(y)	33.5	61.4	64.7	67.9	71.3	74.7	78.0	81.3
AVERAGE AGE AT ATB								
(y)	28.5	16.4	14.7	12.9	11.3	9.7	8.0	6.3

* Restricted to persons with known DS86 dose

Note: ATB = at the time of the bombing

Continued follow-up together with advances in analytical methods are making it possible to address more complex issues than in the past. RERF researchers are developing alternatives to the time-constant (given sex and age at exposure) relative risk models that play a central role in current descriptions of radiation effects on solid cancer risks. These alternative models help to quantify uncertainties in current risk estimates, especially for those exposed as children, and may provide useful insights into the nature of radiation carcinogenesis.

Current data suggest that leukaemia risks for those exposed as adults have persisted throughout life, whereas excess risks for those exposed as children have decreased with time. In view of the complex pattern of excess leukaemia risks following radiation exposure, continued assessment is necessary for complete understanding. Additional follow-up is also necessary to clarify the nature of excess risks for myeloma and lymphoma.

The first comprehensive analysis of the LSS cancer incidence data was published in 1994. These data represent an important complement to the cancer mortality data. Despite the shorter follow-up period for solid cancer incidence (since the tumour registries did not start operation until 1958), the number of cancer cases is greater than the number of deaths. The incidence data provide risk estimates for cancers with lower fatality rates, such as breast, thyroid and skin, than most other cancers and help to clarify the situation for cancers like liver cancer for which death certificate information is often incomplete or inaccurate. A priority is the development of procedures that will allow the unification of the incidence

and mortality data. The tumour registry incidence data already are being used as the basis for a number of site-specific incidence studies, and increased use of data on cancer incidence in the LSS should be used as the basis for case-control studies.

As evidenced by the attention focused on the Sellafield (UK) leukaemia cluster, issues related to the heritable effects of radiation exposure are of great public and scientific concern. The RERF first-generation (F_1) cohort of children of the atomic-bomb survivors is the most powerful epidemiological study able to address whether excess cancer or non-cancer risks result from parental exposures. To date, no evidence of excess risks exists. However, cohort members are relatively young (with an average age of 39 in 1995), so several more decades of follow-up will be necessary to obtain a reasonable assessment of cancer risks (or the lack thereof) in this population. There is increased attention being devoted to this issue by international radiation protection programmes, and the RERF prospective study will provide hard data independent of theoretical considerations.

The value of AHS is in studying the modifying effects of other factors, as well as looking at non-radiation effects generally. The most important epidemiological role of the AHS programme is monitoring of non-cancer diseases that will subsequently result in mortality, such as atherosclerotic diseases and chronic liver diseases, the incidence of which seems to be increased by radiation exposure. New approaches to study these diseases are being introduced.

With a collection of 110,000 frozen samples of serum, it is possible to go back in time to determine if specific confounders, such as homocysteine levels (recently implicated in coronary disease), hepatitis C or other infections may have influenced the course of the above mentioned diseases. The clinical programme also serves as the source of cell collection for the genetics, cytogenetics, and radiobiology studies and more recently for the collection of teeth for the ESR dosimetry analysis.

While results to date show that the human genome is not unusually sensitive to irradiation and indeed may be less sensitive than that of the laboratory mouse, further studies are needed to resolve the issue. No systematic clinical examinations of the offspring (F_1) have occurred since their first year of life. The majority of both dominant disorders and multifactorial inherited diseases are manifest after the first decade of life and, in the latter case, usually after adulthood. A feasibility study in this

area would be of considerable benefit. Based on the very high participation rate, 75-80%, of the children of the survivors during the period 1976-84, when the cytogenetics and protein studies were undertaken, an enthusiastic response from them may be expected. There is an indication that the offspring are anxious about possible health effects since media reports on other radiation-related studies arouse concerns.

A well-designed clinical study of the F_1 cohort using currently available screening methods to identify better defined sentinel phenotypes could provide useful information about genetically based detriment to health and there should be consideration of the feasibility of such a study. This may best be done by convening a workshop on the topic. We believe that during the next two decades, it will become clear whether subsequent generations (F_2) need to be studied, so that at present we do not recommend their study.

Molecular studies in genetics should determine whether mutations were transmitted to the progeny at a variety of genetic sites and what the molecular changes are. The cytogenetic study of parent lymphocytes is recommended to substantiate the theoretical DS86 doses.

The work on radiobiology should concentrate on the analytical studies of the changes at the molecular level involved in tumour development. There is rapid advancement around the world in molecular biology and these developments should be used to focus on the mechanisms of radiation-induced oncogenesis so as to better quantify the risks of low doses of radiation.

We recommend that the LSS research programme should continue until the survivor cohort has died, so as to provide an authentic and complete assessment of the neoplastic and non-neoplastic effects of radiation. We also recognise that there are both medical and social aspects of the AHS that are of direct benefit to the promotion of the health of the A-bomb survivors and their offspring.

RECOMMENDATION 13

We recommend consideration be given to further investigation into the health of the offspring (F_1 cohort) since it may well yield valuable information on genetic effects, especially when conducted together with research using the new molecular genetics techniques.

RECOMMENDATION 14

We recommend that the recently initiated work on the molecular mechanisms of carcinogenesis should be focussed to elicit the shape of the dose-response curve at low doses of radiation.

RECOMMENDATION 15

RERF has a valuable source of surgical and autopsy specimens and of serum, plasma and lymphocyte samples and we recommend that an explicit policy be developed over the management and ethics of the provision of biological samples for use in research, especially outside RERF.

6. STRATEGIC PLANNING AND PROGRAMME MANAGEMENT

While the work of the various scientific departments within RERF has generally been effective and in some areas particularly impressive, there are signs that progress has recently been hampered by severe pressure on professional resources, a situation which we understand is likely to prevail to some extent in future. It is very important therefore that attention is given by the RERF management to the development of long term forward planning processes to achieve the best outcomes within the available budget.

The overall goals and objectives presented to the Panel and the research strategies adopted to reach these goals correctly reflect well RERF's charter. They have evolved over time, drawing on the recommendations of successive reviews and on the outcomes of a series of *ad hoc* workshops in particular fields. The Board of Directors is to be commended for the initiatives it has taken in the past to ensure that the organisation's research strategies are kept up to date with advances in the relevant sciences. In the present times, however, it is normal to take forward planning much further and for management to identify more clearly their programmes, the sub-programmes and projects which fit within them, their relative priorities and the resource obligations which go with them.

Planning can take many forms, but its essential ingredient is to provide a stable framework over (say) a five year time span, against which corporate decisions regarding priorities and resource allocations can be

made, which best reflect RERF's goals. A strategic plan should be forward looking and flexible enough to take into account changes as projects within each Department develop and reach defined milestones or point towards sensible changes in direction. One of its important functions should be to establish for each of the Departments a stable level of core funding, so that programme managers can confidently plan over a five year horizon. We would expect that each passing year would see the updating of a five year "rolling" strategic plan, which accommodates to progress over time, and introduces new aspects as they become relevant.

Perhaps a good illustrative example of the need for global setting of priorities is the assessment of the role and the provision of adequate resources for the Department of Statistics. The Panel was advised that this Department provides expert guidance throughout the organisation, especially to the Departments of Epidemiology and the Department of Information Technology, and in addition has the further responsibility for the understanding and interpretation of the DS86 dosimetry. During the recent period of financial stringency, this Department has endured at least the same degree of attrition and financial constraint as the other Departments, yet deficiencies in this area may have a disproportionate impact on the productivity of the entire organisation. RERF will need to examine its role carefully, since issues such as this can only be addressed by the senior management.

Programme management requires a certain amount of formality to ensure the regular tracking of projects against planning targets and agreed milestones as well as the airing of proposals for new or modified projects. An integral part of this is the periodic external assessment of all sub-programmes and projects. The Panel was advised that the present processes for external scrutiny, carried out by the RERF Science Council, are limited and insufficient for detailed assessment and guidance.

At the Departmental level, there would be a need to review annually with the Chief of Research the progress of individual projects against agreed milestones, to make adjustments where necessary, to set further milestones where appropriate and to foreshadow new directions which projects and the programme may follow.

An additional mechanism, which has been found to work well, is the formation of an internal review panel, involving senior staff from all of the Departments (including Department chiefs) who, over time, review

projects in each Department against agreed milestones and report their assessments to the Chief of Research. Such a process is helpful also in maintaining an informed understanding amongst the staff of the work of their colleagues in other Departments and a better appreciation of the way in which their own work fits within the broader goals of RERF.

Programme management in a research environment such as RERF requires a deftness of touch to ensure that the processes are not so formalised and heavy handed that they obstruct the development of new ideas. Nevertheless, it has been the experience in other establishments that overall strategic planning and a firm commitment to fairly detailed programme management is needed to secure the best outcomes in the present (worldwide) climate of constrained resources. In practical terms, the plan will reach down to the individual Departments, which will need to articulate their own priorities and plans to manage their own programmes, in accordance with the general strategic goals. The process is an interactive one, with the experience and thinking of the Departments contributing to and sharing ownership of the overall strategic plan.

It is important for the continued productivity and success of the RERF programme that external peer review on an intensive basis be established, with a committee of experts chosen from each discipline to review each of the programmes once every five years. The external review committee should have time to assess individual protocols, to review them in concert with the investigators, and then to make recommendations about the future direction of the programme. This mechanism would not only stimulate investigators to improve their projects by exposing them to concentrated critique and discussion with outstanding experts in the field, but would also encourage them to discontinue projects that seemed non-productive.

In the context of the current organisational structure, we recommend that successive five-year Strategic Plans, with annual updates, be developed and offered through the Executive Committee for approval by the Board of Directors.

We also recommend a new peer review process be established with multinational teams reviewing each Department every five years, each team being chaired, for example, by a different member of the Science Council.

We recommend that the Science Council takes a more active role with a closer involvement in the assessment and guidance of RERF. Its membership should reflect all of the major disciplines involved in the work of RERF. We further recommend that appointment to the Council be for 5 year terms, with no more than a single reappointment, and that two members retire each year.

Currently, there is a group of strong and effective leaders and well trained support staff at RERF. A stable cadre of personnel, with the flexibility and capacity to replace those lost by attrition (especially in Statistics and Epidemiology), is essential. One of the problems of RERF inheres in the culture of Japanese institutions, whereby a relatively fixed cohort of workers is predictable because of lifetime guarantees of jobs. This obviously has its strengths, but it also has its limitations, both in preventing RERF from responding quickly, and in limiting personnel openings to new developments in basic science that may have an impact on the RERF programmes. It would be advantageous for RERF if a process could be established for short-term appointments from within Japan, possibly through collaboration with the universities.

In particular, stronger links with universities or other research institutions, especially the universities at Hiroshima and Nagasaki, may be appropriate. These would provide the possibility of PhD students becoming involved in RERF research activities since there are sufficient data for a number of original research studies. Links could be foreseen with mathematical, physical, biological, epidemiological and medical sciences on both radiation and non-radiation related research. In comparison to Hiroshima, some links already exist between RERF Nagasaki and Nagasaki University, with papers being co-authored by staff from both organisations.

The Governor of Hiroshima Prefecture is considering the construction of a cancer centre in Hiroshima city. Were this to proceed, participation in the planning by RERF would be profitable for the conduct of future work in epidemiology and clinical studies.

Work on particular projects may be funded from research fellowships in Japan or, for example, from the Research Directorate of the European Commission (EC). The EC has a research programme into the health effects of ionising radiations which already involves support for projects in the former Soviet Union. Coordination with the work at RERF would seem logical to share scarce expertise from RERF and to try to elicit confirmatory data from other potential databases of occupationally or publicly exposed groups at Chelyabinsk and Mayak. By so doing, the Panel believes, RERF would become internationalised with support from Japan, Europe and the US. A particular problem that was described to the Panel and that particularly affects US cooperation, is the lack of career prospects in the US for those who return from a period at RERF. The Panel believes that this contrasts with the situation in the European Union where such practices are common.

The Panel considers that it is not profitable and indeed positively inefficient for the practice to continue whereby within a single year somewhat in excess of 100 scientists can be imposed upon RERF for 2 or 3 days each. They learn an insufficient amount and distract the staff from their research programmes. A more structured exchange of fewer staff for longer periods would be an improvement, but careful selection of apt fellows is vital.

While RERF is internationally known as a centre for radiation research, the results of its diverse programmes need to be more widely disseminated both in Japan and in the global scientific community. In order to continue the core research programmes of RERF, as well as the collaborative studies, recruiting and maintaining a strong and motivated scientific staff is a vital objective. It would be advantageous to seek short term appointments from other institutions in Japan, as well as to strengthen interactions with universities, especially those in the locality, and to enter into some additional formal overseas arrangements.

RECOMMENDATION 19

We recommend that consideration be given to formal links being established, or strengthened, to universities or other research institutions in Japan and especially to the universities in Hiroshima and Nagasaki, with RERF Department Chiefs having visiting or part-time Professorships and undertaking teaching commitments together with PhD students being involved on projects at RERF.

RECOMMENDATION 20

In addition to the bilateral arrangements between Japan and the US, we recommend that consideration be given to RERF entering into formal programmes of exchange of research fellows with other countries, and with regional or international bodies.

RECOMMENDATION 21

We recommend that, in view of the accumulated knowledge at RERF, it be developed as an Information Centre to promote informed public understanding of the risks of radiation.

The population studies at RERF are unique not only because of the type of exposure received by such large numbers of subjects, but also because the quality of the information recorded about each individual is extremely high. It seems unlikely that a comparable opportunity to study the effects of ionising radiation on health in such a detailed way will present itself in the future: and even if it does, it will take 50 years to accrue as much information as now exists at RERF.

The data held by the Departments of Epidemiology are of enormous importance, not only for assessing the effects of radiation on health, but also for determining the influence of various lifestyle factors on health and their interactions with radiation exposure. There is currently insufficient effort available to analyse the data and present reports, and much of the potentially valuable information collected has so far not been fully utilised.

We recommend that the Departments of Epidemiology should continue to collect data on mortality and cancer incidence and that they be strengthened. The management of RERF should give these studies the highest priority in view of the size and scope of the data. In addition,

research should be carried out by collaborating with epidemiologists from other institutions both in Japan and elsewhere, so that the full range of potentially valuable information already collected can be analysed.

Highly successful work has been performed in the Department of Statistics, which is a source of great strength for the entire organisation. Its input has been essential in making the accumulated data sets the worldwide basis for the estimation of human radiation risks.

We recommend that the Department of Statistics should continue to produce analyses of the risks of radiation exposure in collaboration with the Epidemiology Departments and that the high quality of the research in the Statistics Department be maintained.

We recommend that the Department of Statistics should continue to make available basic data sets on mortality and cancer incidence for analysis by other groups. This should now be extended to making available those data sets relating to mental retardation, IQ, and related outcomes of exposure *in utero*.

Efficient data management and computing are the backbones to the success of research at RERF. The Panel believes that RERF has taken the right strategic decisions with respect to computing infrastructure, and the Department has gone about implementing them with considerable skill and intelligence. Impressive progress has been made over the last few years in creating a central linked database.

We recommend that strong support continue to be given to the Department of Information Technology because it is essential that the large body of data collected over many decades is properly stored, documented and accessible to researchers at RERF.

The importance and merit of the research lies largely in the size and quality of follow-up of the LSS and AHS populations, the quality of the epidemiology and statistics as they relate to the LSS and AHS groups, and the continuing assessment of *in utero* exposed survivors. The role of the Departments of Clinical Studies is central to attaining many of the goals of all divisions.

The content and quality of the research lies in the collaborative role that the Departments play with all other Departments:

by providing clinical data on fatal and non-fatal carcinomas and on non-cancer effects of radiation exposure;

by enabling in-depth investigations of associations to be observed in the LSS;

by furnishing a unique pool of serum, plasma and lymphocyte samples; and

by providing an essential "bridge" function to the survivors.

We recommend that while many of the Clinical Studies projects under way should be extended, the programme should be critically reviewed so that those which are not promising are discontinued. The continuing surveillance of the cohort who were children in 1945 and are now adults is likely to be revealing, since radiation sensitivity may be highest in the young.

We recognise that the AHS is vital to the wellbeing of the survivors and we recommend that this important service continue, since we believe it has led to their high level of cooperation with RERF. As the population ages, and health problems become more complex, consideration needs to be given to ensuring that the voluntary participation remains high.

While molecular biology investigations will enable the most detailed determinations to be undertaken, and will thus be the focus of future work, there is nevertheless need to continue - and even to extend - the more conventional studies of the health of the offspring (F_1 generation). They will also have continued importance because it remains uncertain at what point molecular studies can come sufficiently close to the resolution of the problem of multifactorial hereditary damage produced by radiation.

It does now appear that there can be a more complete chain linking the evolving physics dosimetry and individual data on location at the time of the bombing to chromosome data, to tooth data, and data from solid state dosimetry on other objects, such as building materials, ceramics, or jewellery. While dosimetry has traditionally not been the task of RERF, these new interconnections will be very important for validating the DS86 dosimetry system.

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We recommend that the recently initiated work on the molecular mechanisms of carcinogenesis should be focussed to elicit the shape of the dose-response curve at low doses of radiation.

RERF has a valuable source of surgical and autopsy specimens and of serum, plasma and lymphocyte samples and we recommend that an explicit policy be developed over the management and ethics of the provision of biological samples for use in research, especially outside RERF.

Programme management in a research environment such as RERF requires a deftness of touch to ensure that the processes are not so formalised and heavy handed that they obstruct the development of new ideas. Nevertheless, it has been the experience in other establishments that overall strategic planning and a firm commitment to fairly detailed programme management is needed to secure the best outcomes in the present (worldwide) climate of constrained resources. In practical terms, the plan will reach down to the individual Departments, which will need to articulate their own priorities and plans to manage their own programmes, in accordance with the general strategic goals. The process is an interactive one, with the experience and thinking of the Departments contributing to and sharing ownership of the overall strategic plan.

It is important for the continued productivity and success of the RERF programme that external peer review on an intensive basis be established, with a committee of experts chosen from each discipline to review each of the programmes once every five years. The external review committee should have time to assess individual protocols, to review them in concert with the investigators, and then to make recommendations about the future direction of the programme. This mechanism would not only stimulate investigators to improve their projects by exposing them to concentrated critique and discussion with outstanding experts in the field, but would also encourage them to discontinue projects that seemed non-productive.

In the context of the current organisational structure, we recommend that successive five-year Strategic Plans, with annual updates, be developed and offered through the Executive Committee for approval by the Board of Directors.

We also recommend a new peer review process be established with multinational teams reviewing each Department every five years, each team being chaired, for example, by a different member of the Science Council.

We recommend that the Science Council takes a more active role with a closer involvement in the assessment and guidance of RERF. Its membership should reflect all of the major disciplines involved in the work of RERF. We further recommend that appointment to the Council be for 5 year terms, with no more than a single reappointment, and that two members retire each year.

While RERF is internationally known as a centre for radiation research, the results of its diverse programmes need to be more widely disseminated both in Japan and in the global scientific community. In order to continue the core research programmes of RERF, as well as the collaborative studies, recruiting and maintaining a strong and motivated scientific staff is a vital objective. It would be advantageous to seek short term appointments from other institutions in Japan, as well as to strengthen interactions with universities, especially those in the locality, and to enter into some additional formal overseas arrangements.

We recommend that consideration be given to formal links being established, or strengthened, to universities or other research institutions in Japan and especially to the universities in Hiroshima and Nagasaki, with RERF Department Chiefs having visiting or part-time Professorships and undertaking teaching commitments together with PhD students being involved on projects at RERF.

In addition to the bilateral arrangements between Japan and the US, we recommend that consideration be given to RERF entering into formal programmes of exchange of research fellows with other countries, and with regional or international bodies.

We recommend that, in view of the accumulated knowledge at RERF, it be developed as an Information Centre to promote informed public understanding of the risks of radiation.

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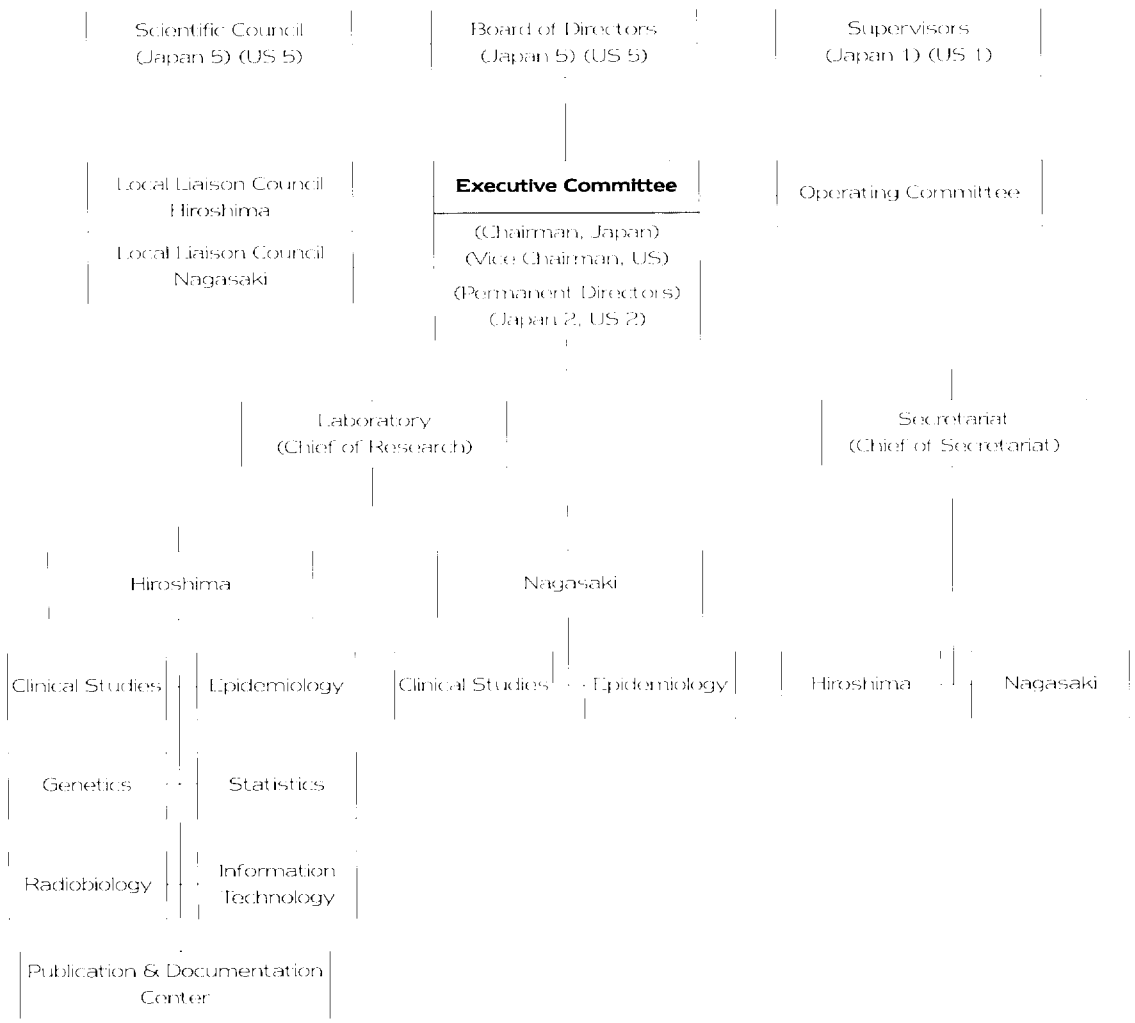
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